The SMART study

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Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM, SMART Study Group. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. *Chest* 2006;129:15-26.

Research question

Does the addition of the long-acting ß-agonist (LABA) salmeterol to asthma therapy increase the risk of respiratory- or asthma-related adverse events or death?

Type of article and design

Twenty-eight week, randomized double-blind, placebo-controlled observational study

Relevance to family physicians

Asthma is a common condition seen in primary care, requiring a clear understanding of the safe and appropriate use of multiple treatment strategies. In 2005, more than 80% of prescriptions for asthma medications in Canada were written by GPs and FPs.[1] Although use of ß-agonists to treat asthma is ubiquitous and appropriate, it has long been fraught with controversy. When overused, the short-acting agents have been associated with increased asthma mortality.[2,3] More than a decade ago, a postmarketing surveillance study implicated LABAs by demonstrating a small, non-significant increase in asthma-related deaths with regular use of salmeterol compared with salbutamol.[4] The SMART trial was designed to assess the safety of salmeterol but was halted after an interim analysis revealed excess mortality and life-threatening respiratory events in the active treatment group.

Overview of study

The SMART study was a multicentre, randomized double-blind, placebo-controlled, observational study. Subjects were eligible if, in the opinion of the investigator, they suffered asthma, if they were receiving at least 1 prescription asthma medication, and if they were at least 12 years of age; LABA users were excluded. Subjects were randomized to receive 42 µg of salmeterol twice daily or placebo, by metered dose inhalers, in addition to their usual asthma therapy for 28 weeks. Subjects attended a single clinic visit to have their eligibility assessed, to provide consent and baseline data, and to be randomized. Subsequent follow-up was conducted by telephone every 4 weeks. The primary end point was occurrence of combined respiratory-related deaths or life-threatening episodes, defined as those requiring intubation and ventilation. Secondary end points included various individual events, deaths due to asthma, and all-cause mortality.

Results

Between 1996 and 2003, 26 355 subjects were randomized to salmeterol or placebo. The population had poorly controlled asthma, with visits to emergency rooms and hospitalizations reported in 26% and 8% of patients respectively during the previous year; 61% had nocturnal symptoms at least weekly. Less than half the population reported using inhaled corticosteroids (ICSs). African-Americans made up about 18% of the subjects; they had more severe disease, and only 38% were using ICSs.

In the overall population, a small non-significant increase in the primary end point was noted in the salmeterol group (relative risk [RR] 1.33, 95% confidence interval [CI] 0.91–2.14). Statistically significant differences were noted in the secondary end points of asthma-related (RR 4.37, 95% CI 1.25–5.34) and respiratory-related deaths (RR 2.16, 95% CI 1.06–4.41) and combined asthma-related death or life-threatening episodes (RR 1.71, 95% CI 1.01–2.89). These differences were largely driven by the African-American population where a statistically significant difference was also noted in the primary end point (RR 4.10, 95% CI 1.54–10.90). No statistically significant differences were noted in the white population in any end point.

Post hoc analysis revealed that using ICSs had a powerful effect on results. No significant differences were noted in the primary or secondary event rates for the overall population reporting baseline use of ICSs. Similarly, for the African-American population, statistically significant differences were noted only in those reporting no baseline use of ICSs. The study was not designed or powered to examine this interaction.

Analysis of methodology

For the first 3 years, subjects were enrolled through a national US advertising campaign and assigned to an investigator in their geographic area. Only a single clinic visit was scheduled, at which time subjects were given 7 canisters of salmeterol or placebo to be used with metered dose inhalers and instructed to use 2 inhalations twice daily in addition to their usual therapy. No further clinic visits were scheduled. Other than providing albuterol metered dose inhalers for subjects not

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taking short-acting ß-agonists, no further medical care was offered. Follow up was by monthly telephone calls only, without reinforcement of compliance with study or baseline medication. Physicians managing patients with asthma will recognize that effectively, for many subjects, this is tantamount to prescribing salmeterol monotherapy, a strategy previously suspected to be hazardous.[4]

Application to clinical practice

Although results of this large observational trial are consistent with results of an earlier surveillance study suggesting a possible hazard associated with use of LABAs, they are contrary to results of many large, well-designed studies demonstrating the benefit of ICS-LABA combination therapy in severe asthma exacerbations or events. For example, salmeterol-fluticasone combined inhaler therapy achieved significantly better guideline-defined asthma control and exacerbation rates compared with fluticasone alone.[5] Similarly, the addition of formoterol to budesonide reduced severe asthma exacerbations by about 50% in patients with persistent asthma.[6]

In a study of fomoterol-budesonide used as both maintenance and reliever therapy, the combination reduced the risk of asthma exacerbation by about 45%.[7] No studies of ICS-LABA combination therapy have demonstrated hazards in asthma. The SMART trial indicates that the addition of LABAs to the therapeutic regimen of patients with poorly controlled asthma worsens outcomes, mainly in African-Americans and those not using ICSs. Although it is possible that African-Americans have genetic characteristics that predispose them to adverse effects from LABAs, it is more likely that the effect is due to less use of ICSs by African-Americans in the study population.

BOTTOM LINE

- Long-acting ß-agonists (LABAs) should not be used as monotherapy in asthma.
- Consistent with current guidelines, LABAs should be given to patients with asthma only after failure of optimal dose and delivery of inhaled corticosteroids (ICSs), as maintenance therapy.
- Combination inhalers that include both ICSs and LABAs are preferred over individually prescribed devices.
- No studies of ICS-LABA combination therapy have demonstrated hazards for patients with asthma.
- The ICS-LABA combination remains the most effective strategy for preventing severe asthma exacerbations in those with persistent asthma.
- African-Americans might be predisposed to severe asthma-related adverse events while taking LABAs and should be monitored closely.

POINTS SAILLANTS

- Les bêta agonistes à action de longue durée (BALD) ne devraient pas être utilisés en monothérapie pour l'asthme.
- Selon les lignes directrices actuelles, les BALD ne devraient être prescrits aux patients asthmatiques qu'après l'échec d'une dose et d'une administration optimales de corticostéroïdes inhalés (CSI), comme thérapie de maintien.
- Les inhalateurs combinés qui contiennent à la fois des CSI et des BALD sont préférables à la prescription de deux inhalateurs individuels.
- Aucune étude sur la polythérapie aux CSI et aux BALD n'a démontré de dangers en cas d'asthme.
- La polythérapie aux CSI et aux BALD demeure la stratégie la plus efficace pour prévenir de graves exacerbations de l'asthme chez les personnes souffrant d'asthme persistant.
- Les Afro-Américains pourraient être prédisposés à des effets indésirables graves reliés à l'asthme quand ils prennent des BALD et doivent donc faire l'objet d'une surveillance étroite.

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